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(54) Treatment of asthma with vitamin D3 derivatives

(57) The use of vitamin D_3 analogues for the treatment of asthma wherein the active agent is chosen from the following 1,25-dihydroxy vitamin D_3 derivatives:

(a) as disclosed in WO - 87/00834 - A1,

(b) as disclosed in WO - 89/10351 - A1,

(c) 24-homo- and 26-homo-1α,25-dihydroxyvitamin D_3 and their 22,23-didehydro-analogues,

(d) 20-oxa-21-nor-1α,25-dihydroxyvitamin D_3 and 22-oxa-1α,25-dihydroxyvitamin D_3,

(e) 26,27-dimethyl and 26,27-diethyl-1α,25-dihydroxyvitamin D_3, and 24,24-difluoro-24-homo-1α,25-dihydroxyvitamin D_3.

The preparations used may be dispensed in a spray can, nebulizer or atomizer.

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NOVEL TREATMENT

This invention relates to the use of certain Vitamin D analogues in the preparation of a pharmaceutical preparation for the treatment of asthma.

Bronchial asthma encompasses a broad spectrum of clinical features, making it difficult to provide a generally acceptable definition of the disease. Reversible airflow obstruction has been used as a physiological index, but there may be asymptomatic periods requiring little medication to treat acute bronchoconstriction. In recent years, the inflammatory events underlying the pathophysiological element of bronchoconstriction, as well as the two other major indices of asthma, i.e. the late reaction and bronchial hyperreactivity, have attracted considerable attention, and asthma has come to be regarded as an inflammatory disease. This view is supported by autopsy and biopsy studies, showing the pathological correlates of asthma to include mucosal oedema, mucus hypersecretion, epithelial damage and massive airways infiltration with eosinophil and neutrophil granulocytes.

The current hypothesis for the pathogenesis of early and late phase reactions in asthma thus teach, that initial exposure to a suitable stimulus, e.g. allergen, results in activation of mast cells, macrophages, T-lymphocytes and epithelial cells, leading to the release of primary mediators such as prostanoids, leukotrienes, PAF-acether, histamine, 5-hydroxytryptamine, neutrophil and eosinophil chemotactic factors, and interleukin 1 (IL-1). As well as having direct effects on bronchial smooth muscle tone, vascular permeability, mucus secretion and endothelial cell function, some of these mediators recruit secondary effector cells such as neutrophils, eosinophils and monocytes/macrophages. The arrival and activation of these cells may be responsible for the second wave of inflammation.

IL-1 seems to play an important role in these phenomena. Not only may IL-1 be one of the chemotactic signals of the initial phase of asthma; Il-1 is also a potent activator of eosinophil and basophil degranulation, and of T-lymphocytes, which have been shown to be in a state of high activity in severe asthma. Mucosal mast cells are partly dependent on T-cells for functional responses. Furthermore, indirect evidence of a mediator role for IL-1 is provided by the protection yielded by local administration of glucocorticoids. Although these drugs are primarily known as potent inducers of lipocortins, which inhibit the release of arachidonic acid-derived lipid mediators of inflammation, they have also the capacity to inhibit the release of IL-1.

Thus, certain vitamin D analogues, including the active form of vitamin D_3, 1α,25-dihydroxyvitamin D_3 1α,25-$(OH)_2D_3$), which inhibit the formation of and/or antagonise some effects of IL-1, may be of therapeutic value in bronchial asthma.

Preferred vitamin D analogues are those which have only moderate activity on calcium metabolism compared to 1,25-$(OH)_2D_3$, but have retained the ability to interfere with IL-1 formation and action. With such compounds it is possible to treat asthma successfully without having the risk of inducing hypercalcemia.

Examples of such preferred vitamin D analogues for use in the present pharmaceutical preparations are

1) compounds described in international patent application No. PCT/DK86/00081, international filing date 14th July, 1986, International Publication No. WO 87/00834, in particular the compound designated MC 903 (example 5 in said patent application) (confer also Calverley, M., Tetrahedron 43, 4609-4619 (1987); Binderup, L. and Bramm, E., Biochemical Pharmacology 37, 889-895 (1988)),

2) compounds described in international patent

application No. PCT/DK89/00079, international filing date 7th April, 1989, in particular Compound 35 (Example 2), Compound 37 (Example 4), Compound 38 (Example 5), Compound 54 (Example 9), Compound 55 (Example 10), and Compound 59 - LEO Code CB 966 (Example 12)

3) 24-homo- and 26-homo-1α,25-dihydroxyvitamin D_3 (together with their 22,23-didehydro-analogues) (Ostrem, V.K. et al, Proc. Natl. Acad. Sci. USA 84, 2610-2614 (1987)),

4) 20-oxa-21-nor-1α,25-dihydroxyvitamin D_3 and 22-oxa-1α,25-dihydroxyvitamin D_3 (Abe, J. et al, FEBS Letters 226, 58-62 (1987)), and

5) 26,27-dimethyl- and 26,27-diethyl-1α,25-dihydroxyvitamin D_3, and 24,24-difluoro-24-homo-1α,25-dihydroxyvitamin D_3 (Ikekawa, N. et al, Chem. Pharm. Bull. 35, 4362-65 (1987)),

In particular the compound MC 903 is well suited for use in inhalation therapy as the compound is inactivated if it reaches the circulation, and thus only asserts an activity locally in the airway tissue.

The mentioned compounds shall form part of pharmaceutical preparations, which are useful in the treatment of human disorders as described above, and which in addition to the vitamin D analogues in question may contain further active ingredients. The concentration of the active vitamin D analogue will depend upon the choice of compound but will generally be between 0.01 and 100 µg/g.

The preparations of the present invention comprise an active compound in association with a pharmaceutically acceptable carrier therefore and optionally other therapeutic ingredient(s). The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the preparations and not deleterious to the recipient thereof.

The preparations include e.g. those in a form suitable for oral, rectal, parenteral (including subcutaneous,

and intravenous) administration, and in the form as an aerosol, which is the preferred form of administration.

The preparations may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active compound into association with the carrier which constitutes one or more accessory ingredients. In general, the preparations are prepared by uniformly and intimately bringing the active compound into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired preparation.

By the term "dosage unit" is meant a unitary, i.e. a single dose which is capable of being administered to a patient, and which may be readily handled and packed, remaining as a physically and chemically stable unit dose comprising either the active material as such or a mixture of it with solid or liquid pharmaceutical diluents or carriers.

The preferred use is by way of inhalation of powder, self-propelling or spray formulations, dispensed with a spray can, a nebulizer or an atomizer. The formulations, when dispensed, preferably have a particle size in the range of 10 to 100 μ.

Such formulations may be in the form of a finely comminuted powder for pulmonary administration from a powder inhalation device or self-propelling powder-dispensing formulations. In the case of self-propelling solution and spray formulations, the effect may be achieved either by choice of a valve having the desired spray characteristics (i.e. being capable of producing a spray having the desired particle size) or by incorporating the active ingredient as a suspended powder in controlled particle size. These self-propelling formulations may be either powder-dispensing formulations or formulations dispensing the active ingredient as droplets of a solution or suspension.

Self-propelling powder-dispensing formulations preferably comprise dispersed particles of solid active ingredi-

ents, and a liquid propellant having a boiling point below 18°C at atmospheric pressure. The liquid propellant may be any propellant known to be suitable for medicinal administration and may comprise one or more C_1-C_6-alkyl hydrocarbons or halogenated C_1-C_6-alkyl hydrocarbons or mixtures thereof; chlorinated and flourinated C_1-C_6-alkyl hydrocarbons are especially preferred. Generally, the propellant constitutes 50 to 99.9% w/w of the formulation.

The pharmaceutically acceptable carrier in such self-propelling formulations may include other constituents in addition to the propellant, in particular a surfactant or a solid diluent or both. Surfactants are desirable since they prevent agglomeration of the particles of active ingredient and maintain the active ingredient in suspension. Especially valuable are liquid non-ionic surfactants and solid anionic surfactants or mixtures thereof. Suitable liquid non-ionic surfactants are esters and partial esters of fatty acids with aliphatic polyhydric alcohols, for instance, sorbitan monooleate and sorbitan trioleate, known commercially as "Span 80" (Trade Name) and "Span 85" (Trade Name), respectively. The liquid non-ionic surfactant may constitute from 0.01 up to 20% w/w of the formulation, though preferably it constitutes below 1% w/w of the formulation. Suitable solid anionic surfactants include alkali metal, ammonium and amine salts of dialkyl sulphosuccinate (where the alkyl groups have 4 to 12 carbon atoms). The solid anionic surfactants may constitute from 0.01 up to 20% w/w of the formulation, though preferably below 1% w/w of the composition solid diluents may be advantageously incorporated in such self-propelling formulation where the density of the active ingredient differs substantially from the density of the propellant; also, they help to maintain the active ingredient in suspension. The solid diluent is in the form of a fine powder, preferably having a particle size of the same order as that of the particles of the active ingredient. Suitable solid diluents include sodium chloride, sodium sulphate and sugars.

Formulations of the present invention may also be in the form of a self-propelling formulation wherein the active ingredient is present as such in solution. Such self-propelling formulations may comprise the active ingredient, propellant and co-solvent, and advantageously an anti-oxidant stabiliser. The propellant is one or more of these already cited above. Co-solvents are chosen for their solubility in propellant, their ability to dissolve the active ingredient, and for their having the lowest boiling point consistent with these above-mentioned properties. Suitable co-solvents are C_1-C_6-alkyl alcohols and ethers and mixtures thereof. The co-solvent may constitute 5 to 40% w/w of the formulation, though preferably less than 20% w/w of the formulation. Antioxidant stabilisers may be incorporated in such solutions-formulations to inhibit deterioration of the active ingredient and are conveniently alkali metal ascorbates or bisulphites. They are preferably present in an amount of up to 0.25% w/w of the formulation.

Such self-propelling formulations may be prepared by any method known in the art. For example, the active ingredient (either as particles as defined hereinbefore as such or in suspension in a suitable liquid or in solution in an acceptable co-solvent, as appropriate) is mixed with any other constituents of a pharmaceutically acceptable carrier. The resulting mixture is cooled, introduced in a suitable cooled container, and propellant is added thereto in liquid form; and the container is sealed. Alternatively, such self-propelling formulations may be prepared by mixing the active ingredient either in particles as hereinbefore defined or in alcohol solution, together with the remaining constituents of the pharmaceutically acceptable carrier other than the propellant; introducing the resulting mixture, optionally with some propellant, into a suitable container; and injecting the propellant, under pressure, into the container at ambient temperature through a valve which comprises a part of the container and is used to control release of the formulation from it. Desirably, the container is purged by removing air from it at a convenient

stage in the preparation of the self-propelling formulation.

A suitable container for a self-propelling formulation is one provided with a manually-operable valve and constructed of aluminium, stainless steel or reinforced glass. The valve should, of course, be one having the desired spray characteristics of particle size as hereinbefore defined. Advantageously, the valve is of the type which delivers a fixed amount of the formulation on the occasion of each operation of the valve, for example, about 50 to 100 microlitres of formulation in each delivery.

Formulations of the present invention may also be in the form of an aqueous or dilute alcoholic solution, optionally a sterile solution of the active ingredient for use in a nebuliser or atomizer, wherein an accelerated air stream is used to produce a fine mist consisting of small droplets of the solution. A buffering agent and a surface active agent may also be included in such a formulation which should also contain a preservative such as methylhydroxybenzoate.

Preparations of the present invention suitable for oral administration may be in the form of discrete units as capsules, sachets, tablets or lozenges, each containing a predetermined amount of the active compound; in the form of a powder or granules; in the form of a solution or a suspension in an aqueous liquid or non-aqueous liquid; or in the form of an oil-in-water emulsion or a water-in-oil emulsion. The active compound may also be administered in the form of a bolus, electuary or paste.

A tablet may be made by compressing or moulding the active compound optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the active compound in a free-flowing form such as a powder or granules, optionally mixed by a binder, lubricant, inert diluent, surface active or dispersing agent. Moulded tablets may be made by moulding, in a suitable machine, a mixture of the powdered active

compound and suitable carrier moistened with an inert liquid diluent.

Preparations for rectal administration may be in the form of a suppository incorporating the active compound and a carrier such as cocoa butter, or in the form of an enema.

Preparations suitable for parenteral administration conveniently comprise a sterile oily or aqueous preparation of the active compound which is preferably isotonic with the blood of the recipient.

In addition to the aforementioned ingredients, the preparations of this invention may include one or more additional ingredients such as diluents, buffers, flavouring agents, binders, surface active agents, thickeners, lubricants, preservatives, e.g. methyl hydroxybenzoate (including anti-oxidants), emulsifying agents and the like.

The compositions may further contain other therapeutically active compounds usually applied in the treatment of the above mentioned pathological conditions, for instance glucocorticoids, anti-histamines, platelet activating factor (PAF) antagonists, leukotriene antagonists, 5-lipoxygenase inhibitors, anticholinergic agents, methyl xanthines, and β-adrenergic agents.

The oral preparations are formulated, preferably as tablets, capsules, or drops, containing from 0.01-100 µg of the vitamin D analogues or metabolites, per dosage unit.

The present invention further concerns a method for treating patients suffering from asthma, said method consisting of administering to a patient in need of treatment an effective amount of one or more of the above mentioned vitamin D analogues or metabolites, alone or in combination with one or more other therapeutically active compounds usually applied in such treatment. The treatment with the present compounds and/or with further therapeutically active compounds may be simultaneous or with intervals.

In the systemic treatment, daily doses of from 0.1-500 µg, preferably from 0.1-100 µg, of the vitamin D analogues or metabolites are administered.

In inhalation treatment, an amount effective to treat the disorders hereinbefore described depends on the usual factors, such as the nature and severity of the disorders being treated and the weight of the human. However, a unit dose, consisting of one or a number of fixed discharges from the dispensing means, will normally contain 0.1 to 100 µg, for example 1 to 10 µg, of the active compound. Unit doses will normally be administered once or more than once a day, for example 2, 3, 4, 5 or 6 times a day, more usually 2 to 4 times a day, such that the total daily dose is normally in the range, for a 70 kg adult, of 0.6 to 600 µg, for example 1 to 100 µg.

Within the above indicated dosage range, no adverse toxicological effects are observed.

The invention will now be further described in the following non-limiting Examples:

Example 1

Nebulizer solution

	1000 ml solution
MC 903	2 mg
Ethanol absolute	160 g
Potassium dihydrogen phosphate	2 g
Potassium hydroxyde	q.s.
Purified water	to make 1000 ml

MC 903 and potassium dihydrogen phosphate are dissolved in part of the water. pH is adjusted to 7.5, using a sufficient amount of potassium hydroxyde solution.

Ethanol is added together with purified water to make 1000 ml.

The solution is used in nebulizers for inhaling.

Example 2

Nebulizer solution

	1000 ml solution
CB 966	2 mg
Ethanol absolute	160 g

Potassium dihydrogen phosphate	2 g
Potassium hydroxyde	q.s.
Purified water	to make 1000 ml

CB 966 and potassium dihydrogen phosphate are dissolved in part of the water. pH is adjusted to 7.5, using a sufficient amount of potassium hydroxyde solution.

Ethanol is added together with purified water to make 1000 ml.

The solution is used in nebulizers for inhaling.

Example 3

Powder inhaler capsule

	1000 capsules
MC 903	1 mg
Lactose microcrystalline to make	100 g

MC 903 is micronized in a fluid energy mill to a particle size essentially below 5 µm and mixed with the lactose with a particle size mostly between 20 and 60 µm.

The powder mix is passed through a high speed mill and filled in 1000 capsules each containing 1 µg of MC 903.

The content of the capsules is used for inhalation in a powder aerosol device.

Example 4

Pressurized aerosol

	5000 containers
MC 903	1.25 g
Ethanol absolute	9.700 kg
Dichlorotetrafluoroethane	17.000 kg
Dichlorodifluoromethane	39.800 kg

MC 903 is dissolved in ethanol absolute, cooled to -10°C and mixed with dichlorotetrafluoroethane.

After cooling to -40°C the dichlorodifluoromethane is added.

The mixture is filled in aluminium aerosol containers each containing 13.3 g of aerosol mixture.

The containers are closed with metering valves.

Each puff for inhalation will deliver 40 µl of aerosol mixture containing 1 µg of MC 903.

Example 5

Pressurized aerosol

	5000 containers
MC 903	0.5 g
Sorbitan monooleate	0.020 kg
Trichlorofluoromethane	18.200 kg
Dichlorotetrafluoroethane	17.000 kg
Dichlorodifluoromethane	39.700 kg

MC 903 is micronized in a fluid energy mill to a particle size essentially below 5 µm, and suspended in a solution of sorbitan monooleate in trichlorofluoromethane.

After cooling to -50°C the dichlorotetrafluoroethane and dichlorodifluoromethane are added and mixed.

The mixture is filled in aluminium aerosol containers each containing 15.2 g of aerosol mixture.

The containers are closed with metering valves.

Each puff for inhalation will deliver 50 µl of aerosol mixture containing 0.5 µg of MC 903.

Example 6 Capsules containing 22-oxa-1α,25-dihydroxyvitamin D_3

22-oxa-1α,25-dihydroxyvitamin D3 ('22-oxa') was suspended in arachis oil to a final concentration of 5 µg '22-oxa'/ml oil. 10 Parts by weight of gelatine, 5 parts by weight of glycerine, 0.08 parts by weight potassium sorbate, and 14 parts by weight distilled water were mixed together with heating and formed into soft gelatine capsules. These were then filled each with 100 µl of the '22-

oxa' in oil suspension, such that each capsule contained 0.5 µg '22-oxa'.

WHAT WE CLAIM IS:

1. The use of a compound selected from the group consisting of

1) compounds described in international patent application No. PCT/DK86/00081, international filing date 14th July, 1986, International Publication No. WO 87/00834, in particular the compound designated MC 903 (example 5 in said patent application) (confer also Calverley, M., Tetrahedron 43, 4609-4619 (1987); Binderup, L. and Bramm, E., Biochemical Pharmacology 37, 889-895 (1988)),

2) compounds described in international patent application No. PCT/DK89/00079, international filing date 7th April, 1989, in particular Compound 35 (Example 2), Compound 37 (Example 4), Compound 38 (Example 5), Compound 54 (Example 9), Compound 55 (Example 10), and Compound 59 (Example 12)

3) 24-homo- and 26-homo-1α,25-dihydroxyvitamin D_3 (together with their 22,23-didehydro-analogues) (Ostrem, V.K. et al, Proc. Natl. Acad. Sci. USA 84, 2610-2614 (1987)),

4) 20-oxa-21-nor-1α,25-dihydroxyvitamin D_3 and 22-oxa-1α,25-dihydroxyvitamin D_3 (Abe, J. et al, FEBS Letters 226, 58-62 (1987)), and

5) 26,27-dimethyl- and 26,27-diethyl-1α,25-dihydroxyvitamin D_3, and 24,24-difluoro-24-homo-1α,25-dihydroxyvitamin D_3 (Ikekawa, N. et al, Chem. Pharm. Bull. 35, 4362-65 (1987)),

in the manufacture of a medicament for the treatment of asthma.

2. The use according to claim 1, in which the active component is (1S,1'E,3R,5Z,7E,20R)-(9,10)-seco-20-(3'cyclopropyl-3'-hydroxyprop-1'-enyl)-1,3-dihydroxypregna-5,7,10(19)-trien.

3. The use according to claim 1, in which the active component is 1(S),3(R)-dihydroxy-20(R)-(5-ethyl-5-hydroxy-1-heptyl)-9,10-secopregna-5(Z),7(E),10(19)-triene.

4. A topical medicament according to any one of claims 1 to 3, containing the active component in an amount of from 0.01 ppm to 10 ppm of the medicament.

5. The use of a compound as defined in any one of the claims 1 to 3 for the treatment of asthma.

6. The use according to claim 5 of (1S,1'E,3R,5Z,7E,20R)--(9,10)-seco-20-(3'cyclopropyl-3'-hydroxyprop-1'-enyl)-1,3--dihydroxypregna-5,7,10(19)-trien,

7. The use according to claim 5 of 1(S),3(R)-dihydroxy--20(R)-(5-ethyl-5-hydroxy-1-heptyl)-9,10-secopregna-5(Z),-7(E),10(19)-triene.

Patents Act 1977
Examiner's report to the Comptroller under Section 17 (The Search Report)

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Relevant Technical fields

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Search Examiner
J F JENKINS

Databases (see over)

(i) UK Patent Office

(ii) ONLINE DATABASE: CAS-ONLINE

Date of Search
28 JANUARY 1993

Documents considered relevant following a search in respect of claims 1-7

Category (see over)	Identity of document and relevant passages	Relevant to claim(s)
X,Y	WO 89/10351 A1 (LEO PHARMACEUTICAL) see page 5 line 14 to page 6 line 2 and Claim 7	1,3 and 4

Category	Identity of document and relevant passages	Relevant to claim(s.

Categories of documents

X: Document indicating lack of novelty or of inventive step.

Y: Document indicating lack of inventive step if combined with one or more other documents of the same category.

A: Document indicating technological background and/or state of the art.

P: Document published on or after the declared priority date but before the filing date of the present application.

E: Patent document published on or after, but with priority date earlier than, the filing date of the present application.

&: Member of the same patent family, corresponding document.

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